REMARKS

An RCE is being filed herewith.

Claims 1-43 are pending in the present application. Claims 72-8 and 19-43 have been withdrawn from consideration as being directed to on-elected subject matter. Claim 1 has been amended to more explicitly describe the invention. Claims 12 and 18 have been amended to make that which is implicit, explicit. Claim 11 has been cancelled without prejudice or disclaimer. No new matter has been added by virtue of these amendments and their entry is respectfully requested.

Amendment and cancellation of the claims are not to be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed, or substantially similar claims, in this or one or more continuation patent applications.

Claim Rejections Under 35 U.S.C. § 103.

Claims 1, 9-11 and 13-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,235,713 B1 (filed Aug 1997; PTO 892) in view of U.S. Patent No. 5,874,290 (Feb 1999; PTO 892).

Applicants respectfully disagree and traverse the rejection.

The Examiner asserts that:

> The '713 patent teaches a method of detecting VEGF-D in a biological sample comprising the steps of contacting the sample with a probe such as a monoclonal and polyclonal antibody that bind specifically to VEGF-D and detecting the binding by means of a detectable label (see col. 6, lines 66-67 bridging col. 7, lines 1-7, col. 5, lines 51-67, in particular). The reference VEGF-D is a native VEGF-D protein (see col.

> 19, lines 34-42, VEGFD fullFLAG, in particular) and proteolytic cleaves to produce product comprises a VEGF-D homology domain (see col. 19, line 25, VEGFDΔNΔC, in particular). The '713 patent teaches VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk (see col. 6, lines 16-18, in particular).

The Examiner acknowledges that the '713 patent differs from the instant invention in that the '713 patent does not teach or disclose that VEGF-D is detectable in brain tumors, nor does it suggest or disclose that VEGF-D is a potential tumor marker. Applicants submit that the '713 patent provides no disclosure, teaching nor motivation to one of ordinary skill in the art, to examine brain tumors for the detection of the over-expressed X-linked VEGF-D gene in brain tumors. To make the teachings of the instant invention more explicit, Applicants have amended the claims to include reference to the over-expression of the VEGF-D. Further, in response to the Examiner's assertions that the "[t]he '713 patent teaches VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk," Applicants emphasize that **brain tumors**, especially high grade gliomas are non-metastatic tumors, therefore detection of over-expressed VEGF-D in brain tissues is **not** an "indicator of future metastatic risk."

Furthermore, Applicants submit that the VEGF-D peptide disoussed in the '713 patent is not a full length native protein but a fragment from residue 93 to 201 (see, col. 18, lines 66-67). The '713 patent neither teaches nor discloses the detection of native VEGF-D or that it is over-expressed in brain tumors.

The Examiner asserts on page 3 of the Office Action that:

> The '290 patent teaches various VEGF's that have been overexpressed in different types of brain tumors (see col. 3, lines 5-14, and references therein, in particular). The '290 patent further teaches the use of fetal brain tissue and cell lines derived from human glioblastoma multiforme tumor tissue for diagnosis of brain tumor using specific VEGF markers (see col. 43, lines 35-62, in particular).

Applicants respectfully traverse. The '290 patent does not teach over expression of **VEGF-D in glioblastoma's**. The Examiners assertions that "VEGF" is overexpressed in **various** brain tumors is over reaching. The '290 patent does not provide one of ordinary skill in the art any guidance as to which VEGF family, which brain tumor, does over expression of a gene imply over expression of a protein, overexpressed as compared to what? Furthermore, the experimental results do not show that the VEGF2-2 is over-expressed in glioblastoma tumors. The '290 patent does not teach or disclose that VEGF-D is over-expressed in tumors. VEGF was detected in some brain tumors but the '290 patent does not teach or disclose detection and **over-expression of VEGF-D as a diagnostic marker of brain tumors**. Further, the '290 patent does not teach detection of over-expressed VEGF-D in brain tissue samples. The laundry list of tumor cell lines cited by the Examiner do not direct one of ordinary skill in the art to **select a tumor** for detection of over expressed VEGF-D. The '290 patent utilized established cell lines for detection of the D2-2 gene. (See, for example, column 43, lines 49-62). Applicants submit that fetal brain tissue is not a tumor as suggested by the Examiner and consequently cannot be used as a tool to diagnose brain tumors. Considering the complexity of gene expression in cancer, especially genetic and epigenetic influences, the chromosomal localization of the genes and their promoter regions are important factors determining the levels of gene expression of various factors. In addition, the transcribed genes must be translated into proteins and this also occurs in a complex hard to predict manner in cancer cells. Considering that VEGFs have different chromosomal localizations, one of ordinary skill in the art would not expect that just because one type of VEGF is found in cancer, the detection of another factor is expected or obvious. See for example, the '713 patent column 2, lines 10-26. Therefore, the '713 patent in view of the '290 patent do not provide any suggestion, teaching or motivation to combine the teachings and arrive at the instant invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 12 and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,235,713 B1 (filed Aug 1997; PTO 892) in view of U.S. Patent No. 5,874,290 (Feb 1999; PTO 892) as applied to claims 1, 9-11 and 17 and further in view of Stacker et al (J. Biol. Chem. 274(45):32127-32136; Nov 1999; PTO 1449) and Achen et al (Eur. J. Biochem. 267:2505-2515, May 2000; PTO 1449).

Applicants respectfully traverse.

As the Examiner has acknowledged on page 5 of the Office Action, that claim 12 differs from the combined teachings of the references in that the method for detecting a cancer in a brain tissue sample wherein the VEGF-D protein is proteolytic cleavage product comprises a VEGF-D homology domain. Claim 18 differs from the combined teachings of the references that the method for detecting cancer in a brain tissue sample wherein the monoclonal antibody is VD1. However, in order to expedite prosecution, Applicants have amended claims 12 and 18.

Arguments regarding the combined teachings of '713 and '290 have been discussed *supra*, and for the sake of brevity will not be repeated here. Neither Stacker et al, nor Achen et al, standing alone or in combination teach the detection of a VEGF-D homology domain in **brain cancer**. Furthermore, isolation of a bioactive fragment in Stacker et al., does not amount to a diagnosis of glioblastoma multiformae as alleged by the Examiner. Use of a VD1 monoclonal antibody for "analyzing lymphaniogeneis induced by VEGF-D and its contribution to metastatic spread," is irrelevant to the present invention. Since, a normal brain **does not have a lymphatic system** and **GBM does not grow lymphatic vessel**, GBM's **do not metastasize**. Applicants surprising discovery was the ubiquitous detection of the VEGF-D homology domain in the brain. None of the references teach the detection of VEGF-D in the brain nor, was the form of VEGF-D in the brain known prior to applicants invention. As discussed, above, '290 patent does not teach that **VEGF-D is over expressed in brain tumors**, various VEGF's do not amount to detection of VEGF expression in glioblastoma tumors; the link between expression of VEGF in other tumors and the brain that the Examiner is apparently trying to establish is incorrect.

Glioblastomas do not metastasize. Use of the VD1 monoclonal antibody for "analyzing lymphangiogenesis" would not be applicable to a brain tumor for the reasons set forth above. The references of the '290 patent to "different types of brain tumors" has been discussed above, and the '713 patent regarding "future metastatic risk" is inapplicable for the reasons set forth above.

Accordingly, none of the combined teachings teach detection of the proteolytic cleavage product comprising a VEGF-D domain and detection thereof in brain tissue samples by VD1, due to a non-metastatic brain tumor. Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

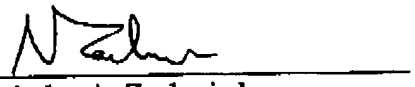
Applicants respectfully request entry of the foregoing remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application with claims 1 and 9-18 define patentable subject matter and are in condition for allowance. Accordingly, Applicant respectfully requests allowance of these claims.

This response is being timely filed within the shortened statutory period. Although, Applicants believe that no extensions of time are required with submission of this paper, Applicants request that this submission also be considered as a petition for any extension of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

If there are any remaining issues or the Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at telephone number shown below.

Respectfully submitted,

AKERMAN SENTERFITT



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